CHRONIC MICROELECTRODE RECORDING ARRAYS

Quarterly Report

(Contract HHSN265200423631C)

January 2005 — March 2005

Submitted to the

National Institute of Neurological Disorders and Stroke
National Institutes of Health

by

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April 2005

CHRONIC MICROELECTRODE RECORDING ARRAYS

Executive Summary

This contract seeks to develop wireless microsystems for chronic multi-channel recording in the motor cortex of primates, setting the stage for subsequent trials in quadriplegic humans. The approach we are taking uses active or passive multi-channel two-dimensional silicon probes containing 16-64 sites each, arranged in three-dimensional arrays. The probe output signals are routed to circuitry on the rim of the implant assembly using multi-lead silicon- or polymer-based microcables. The rim-mounted circuitry identifies neural spikes and passes the spike occurrences to the outside world over a bidirectional wireless link that derives power and control signals for the implant from an externally-supplied RF carrier. The implanted circuitry can also be used to output a full analog representation of the neural activity on any single site.

During the past quarter, we have designed and fabricated new 16-site multi-shank passive probes that are optimized for use in monkey motor cortex. Additional passive probes for use in studies of chronic tissue reaction have also been realized. Our 64-site active probe has been redesigned for non-multiplexed operation and the amplifiers have been optimized for improved dynamic range. They still offer an overall gain of 1000 and bandwidth from an adjustable lower cutoff (1-100Hz) to 10kHz, and they allow site testing on demand.

We have received the test-chip version of our implantable spike detector ASIC back from the MOSIS/AMI foundry and initial tests have shown that the critical circuit blocks are fully functional. We have also completed the design of a bidirectional wireless interface for the probes. This interface extracts power and command signals for the implant from an externally-supplied RF inductively-coupled carrier and transmits neural data back to the outside world over a 100MHz telemetry link with data rates as high as 20Mbps. This interface chip has been submitted for fabrication.

We have redesigned the MINI implant assembly to improve its ability to provide a long-term interface between the external world and the nervous system, scaling it for use in rabbit models. Successful implants over periods of one month have been achieved with the revised devices, and we hope to return to implants in monkey motor cortex during the coming quarter.

During the coming quarter, the new passive probes will be used in-vivo and the redesigned active probes will be fabricated and tested. The analog spike detector chip will be tested and its design will be iterated to produce chips capable of supporting the intended first-year microsystem. The bidirectional telemetry interface chip will be fabricated and returned for testing as well. Work will continue to refine the MINI implant housing and the surgical techniques associated with successful implants in rabbit and monkey models.

Activity Summary

During the past quarter, we have worked to create the various components that will be required to realize wireless implants of 64 recording sites in primate motor cortex. These implants must be fully functional by late fall of this year, and the timeline is thus quite short. Our activities during this past quarter were as follows:

- A paper describing the results of this program was completed for the *IEEE Engineering in Medicine and Biology Magazine*, and a paper on our active probes and digital spike identification chip was presented at the 2005 *IEEE International Solid-State Circuits Conference.* An extended version of the latter paper will also be published in the *IEEE Journal of Solid-State Circuits* later this year.

- A family of passive probes specifically designed for monkey motor cortex has been successfully fabricated. A variety of 16-site single- and four-shank designs were included in this run.

- The design of an iterated version of our 64-site active recording probe was completed. This probe features eight channels with an on-board gain of 1000 per channel. The probe has a non-multiplexed output stage with improved dynamic range and will interface directly with our spike identification chip. The spike identification chip has been fabricated and is now entering test.

- A bidirectional telemetry test chip has been designed and submitted for fabrication. The chip contains circuitry for powering and controlling the implant from energy supplied by a modulated external RF field along with circuitry for outputting the digitized spike information at a rates as high as 20Mbps.

- Scaled-down versions of the microsystem housing have been designed, fabricated and assembled. These designs allow for *in-vivo* testing in rabbits. The scaled-down version is still composed of a polysulphone housing, printed circuit board, and bonded probes. The assembly process was similar to that for the full-scale MINI; however, the percutanous connectors were eliminated.

- *In vitro* tests were performed on the microsystem assembly to characterize the sealing capabilities of the inner lumen in simulated surgical implant procedures. *In vivo* tests were performed in rabbits to evaluate the biocompatibility and toxicity of the materials used (silicon, polysulphone, silicone elastomer), to develop surgical techniques for implanting the MINI and investigate ways to appropriately manage the dura, and to test the long-term durability of the silicon ribbon cables while floating with the brain and supported solely by artificial CSF.

- To aid with insertion of the silicon probes, a prototype insertion tool has been developed and is currently being evaluated.

- A new collaboration has been initiated with a neuropathologist at the University of Michigan. A preliminary pathology report from one monkey implant showed extensive inflammation in the region above the implant site, causing necrosis of the tissue. It is likely this was caused by trauma of the surgical procedure; ongoing experiments are being conducted in rabbits, a more sensitive model.

Challenges:

- We are still optimizing our surgical techniques, especially with regard to managing the dura to prevent dural adhesions. We are currently investigating dural substitutes; however, handling the dura in a delicate fashion is challenging within the confined space of the MINI.

- Insertion of the probes continues to be a challenge due to the limited confinements of the MINI lumen. We are making advances in this area with the surgical insertion tool mentioned above.

Research Results and Discussion

Probe Development

During the past term, a mask set including eight 16-channel probe designs specifically for monkey motor cortex has been successfully fabricated. The single- and four-shank designs have a number of design variations, including holes through the shanks for tissue anchoring and/or seeding, tip and edge sites, and a large site for use as a reference during recording. A subset of the designs is shown in Fig. 1.

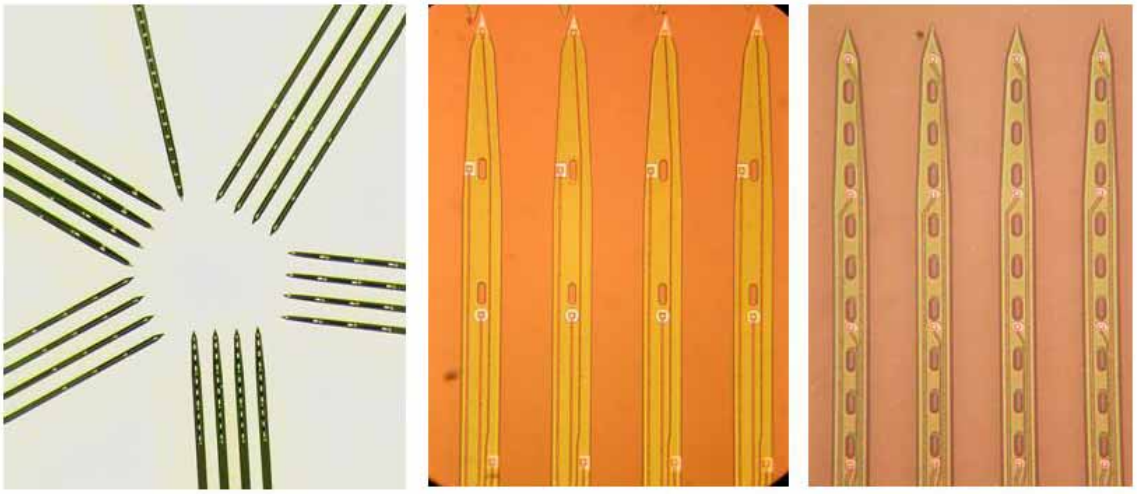


Fig. 1: Probes fabricated for use in monkey motor cortex. The panel on the left shows six of the eight included designs. The panel in the middle shows a probe with sites at the tip and edge of the shanks. The panel on the right shows a probe with many holes through each shank for use in tissue anchoring and perhaps for seeding. Shanks on the four-shank probes are spaced at 250μm. Sites on probes in middle and right panels are spaced at 400μm.

A separate set of probes for use in examining the tissue response to chronically indwelling probes has also been fabricated. These probes are shown in Fig. 2. They consist of a boron-doped silicon frame 6μm wide that provides strength and supports interconnect leads. The overall probe in this case is 40μm wide but over most of its width it is open, allowing tissue regrowth. We hope to see whether such probes appear to the tissue much like a stab wound that can heal and will not evoke the tissue response of solid-shank structures. These will be evaluated in future terms and are representative of the design capabilities of the technology and address problems encountered.

Fig. 2: Back and front views of probes intended for chronic use in the CNS.

The design of a new version of our 8-channel 64-site active probe was also completed during the past quarter. This active probe has a front-end selector that allows selection of eight sites of interest. The selection pattern remains unchanged from our earlier probe. The signals from the selected channels are passed through two stages of amplification, the first having a gain of 100 and the second having a gain of 10, resulting in a 1000X amplification of the neural signals. The functionality of the new amplifiers is the same as for previous amplifiers, including the use of a tuning voltage to vary the lower cutoff frequency. The only major modification made is in the amplifier design. The new amplifiers have an NMOS output stage, resulting in a larger dynamic range at the output compared to previous amplifiers. The simulated dynamic range of the new probe and its predecessor are shown in Fig. 3. The new probe is not multiplexed. Instead, the eight channel outputs will drive the spike detector directly.

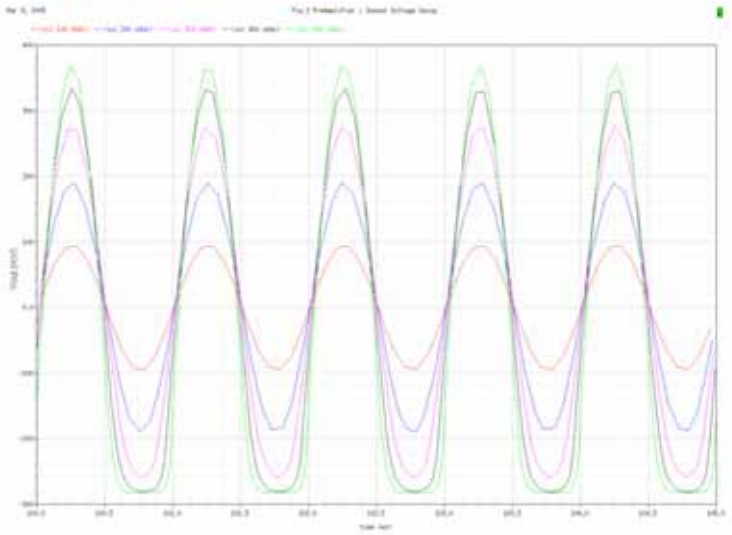


Fig. 3a: Dynamic range of the previous preamplifier (with a PMOS output stage)

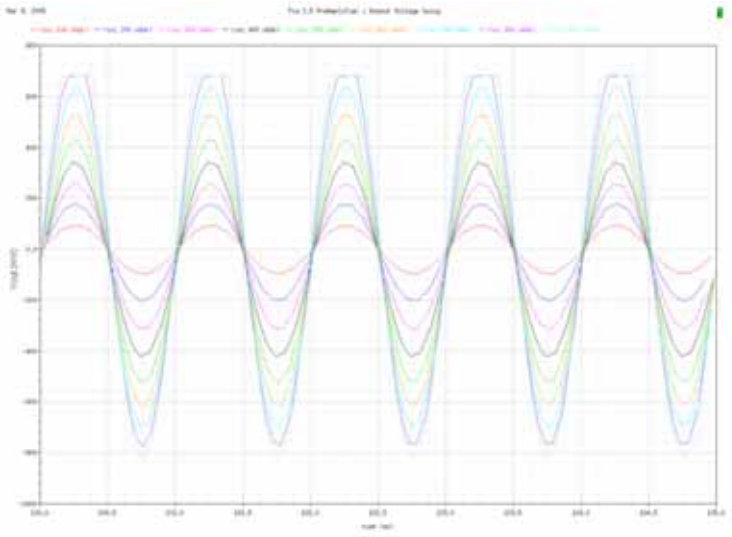


Fig. 3b: Dynamic Range of the new preamplifier (with an NMOS output stage)

The simulation results show that the previous amplifier had a very limited swing in the negative direction (Fig. 3a) while the modified version has enough swing in both directions for the signals of interest. The time-division multiplexer used in the older amplifier was removed so that the analog spike detector unit receives the individual channel signals directly. The new probe also has the ability to measure the site impedances by bypassing the amplifiers. Fig. 4 shows the functionality of the new probe.

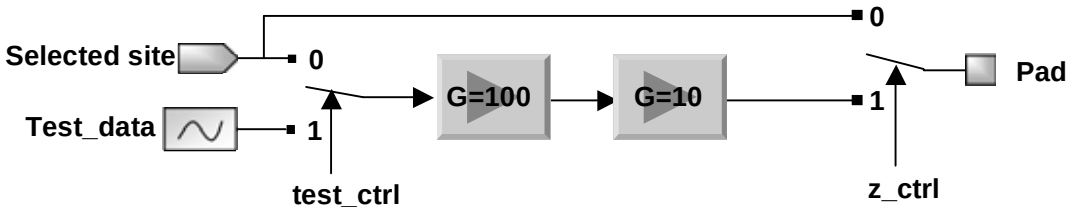


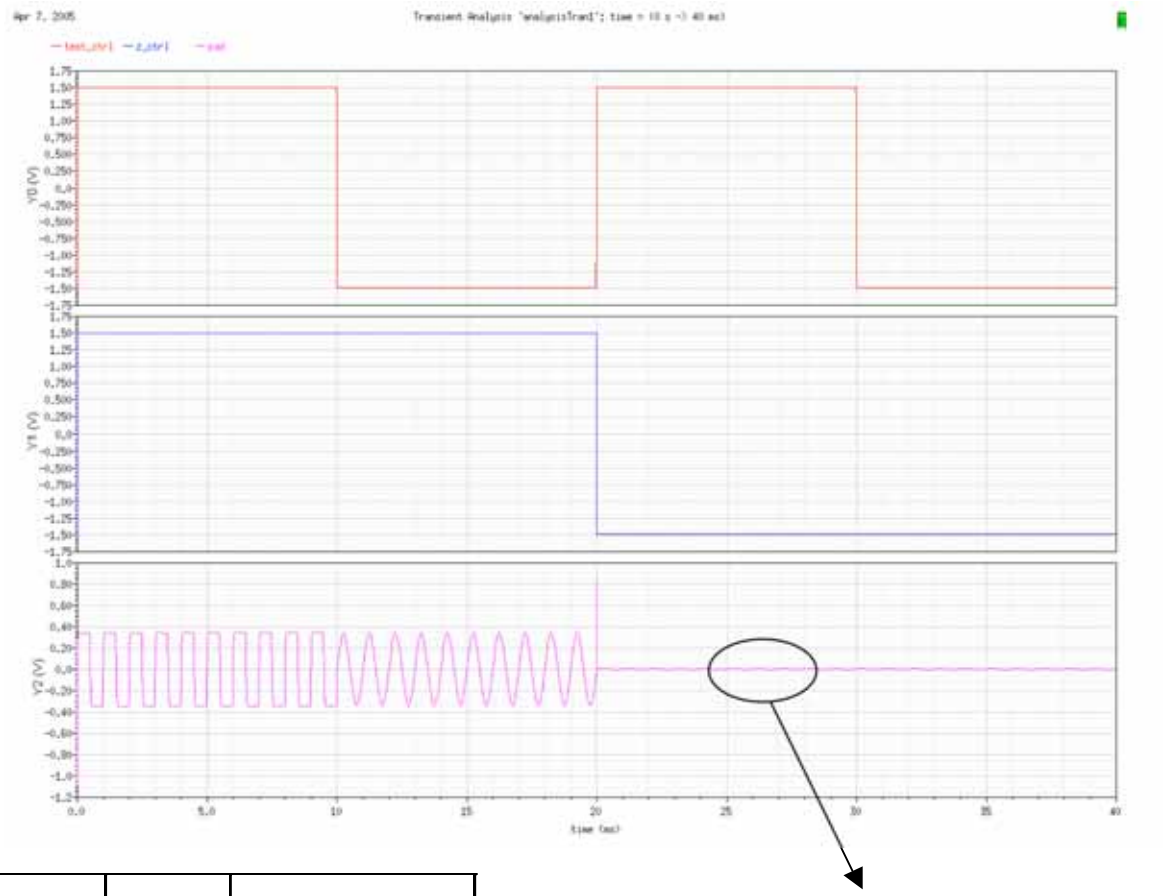
Fig. 4: Block diagram of the circuitry on the new probe.

The circuitry has three modes: site impedance test mode, normal operation mode and amplifier test mode. For the simulations, the test data was chosen as a square wave and the signal applied to the selected site was a sine wave, both with peak amplitudes of 500μV. The simulated results are shown in Fig. 5. The table in Fig. 5 shows the control logic for selecting the desired mode. Fabrication of the new probe will take place during the coming quarter.

Bidirectional Recording Interface

During the past term, we also completed the design of a first version of the bidirectional telemetry chip for the implantable microsystem. Fig. 6 shows a block diagram of the intended multichannel neural recording system, while Fig. 7 shows its wireless interface. The bidirectional telemetry test chip (BTT) generates the regulated power supply required for the system from energy received through an inductive link. It also demodulates the data and recovers the clock that are sent from the outside world through modulations on the inductive carrier. The extracted clock and data are delivered to Data Interpretation and Control Logic (DICL), which forms a compact special-purpose microprogrammed control unit, dedicated to the intended system. Based on the received data, the DICL generates the timing and control signals required to control the other two system modules: the active probes module (APM) and the mixed-signal neural processing unit (NPU), as is dictated by the incoming data packet. There will also be another control unit on the NPU to take care of all the issues associated with the outgoing recorded/ compressed neural data. There is also a back telemetry block on this test chip consisting of an encoder to have the outgoing data accompanied by the associated clock, and the required circuitry to realize digital modulation and transmission of the outgoing neural data. The BTT is designed so that upon the establishment of supply voltages it initializes the system to operate in Scan mode with a specific site selection pattern at the probe front-end. To be controllable from the outside world, it is designed to receive a control word accompanied by parity bits via the telemetry link. Based on the received commands and addresses as the control word, the BTT can perform front-end site selection and also

set the system in either Scan or Monitor mode. Furthermore, the BTT is capable of performing some analog settings in the NPU according to the received control word.



Test ctrl	Z_ctrl	Pad
0	0	signal from selected site (bypass amps)
0	1	amplified signal from site
1	0	signal from selected site (bypass amps)
1	1	send test data through all amplifiers

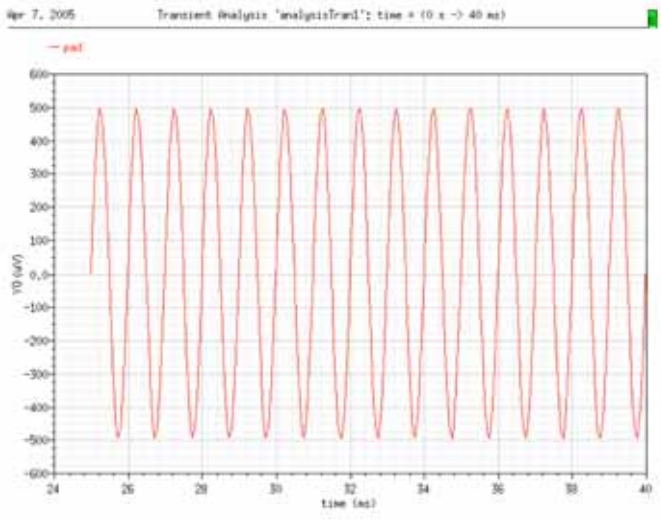


Fig. 5: Simulated results for the new probe circuitry shown in Fig. 4.

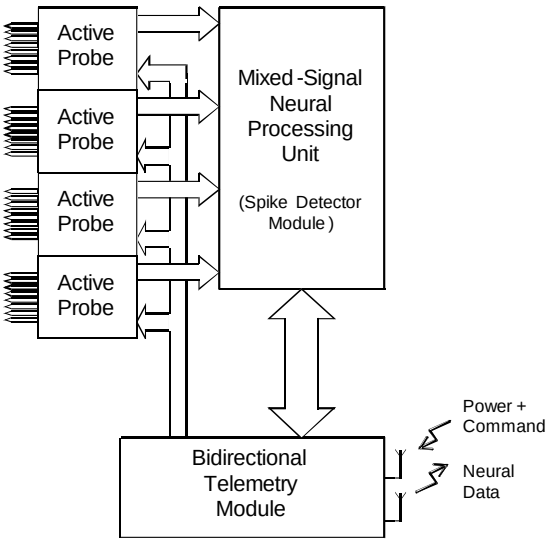


Fig. 6: General block diagram of the neural recording system

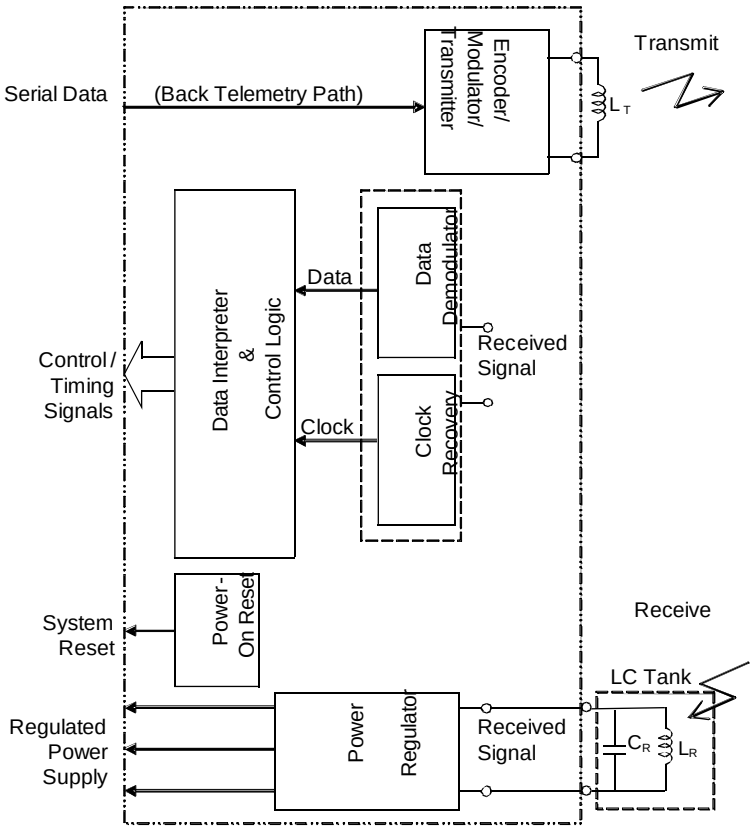


Fig. 7: General block diagram of the BTT

Fig. 8 shows the structure for the data packet transmitted from the outside world to the BTT. Being one of the critical blocks in every telemetry-powered system, the regulated power supply provides ±1.5V voltages with a line regulation of 2mV/V over a 13-V input voltage range and is capable of delivering more than 50mA to a resistive load. The receive link is designed to receive a maximum bit rate of 2Mb/sec. FSK-modulated on an 8-MHz carrier and the transmit (back telemetry) link is capable of sending data with a rate of about 20Mb/sec modulated on a 100-~120-MHz carrier in on-off keying fashion. Fig. 9 shows the simulated waveforms for receive (*Clock Recovery/Data Demodulator*) and transmit (*On-Chip Transmitter*) data paths.

Shown in Fig. 10 is the simulated operation of the DICL block when receiving two consecutive data packets for Site Selection and Monitor Mode, respectively. The topmost signal is the demodulated data coming from data demodulator, and the rest shows some of the internal and output signals. The layout of the whole chip, shown in Fig. 11, measures 4.6mm x 4.6mm and has been submitted to MOSIS for fabrication in the AMI 1.5µm double-metal double-poly standard N-well CMOS process.

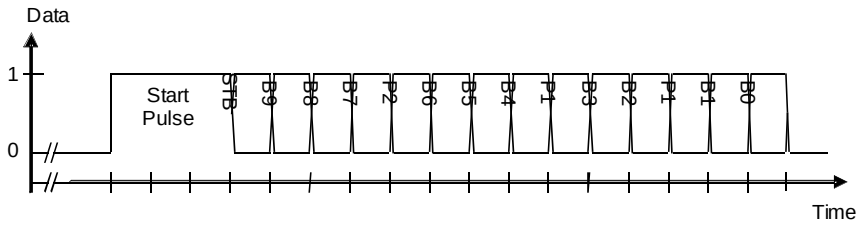
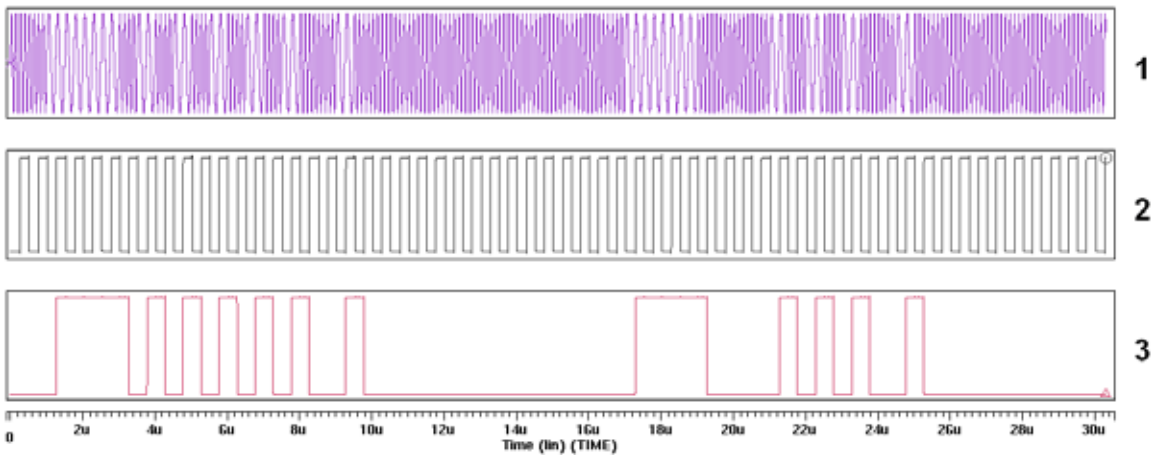


Fig. 8: The structure of the data packet for the wireless interface

A Modified MINI Microsystem Assembly for Rabbit Implantation

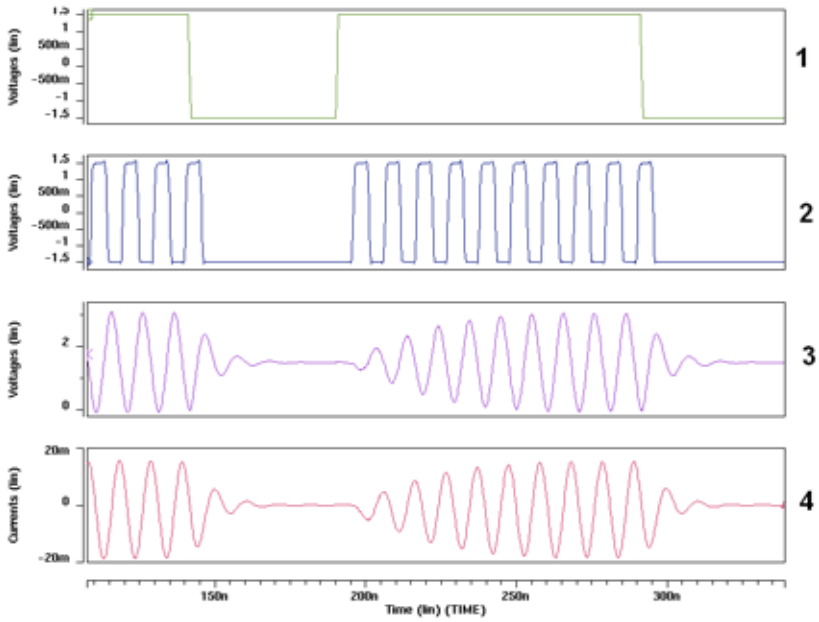
Since we are taking a step back from the monkey implantations to perform a series of more rapid tests in rabbits and refine surgical techniques, the design of the housing was significantly altered into its present design, MINI 3.1 (Fig. 12). The outer diameter of the housing was reduced by approximately a centimeter and a half. This decrease was required to permit the entire setup to fit on the cranium of a rabbit. Due to this reduction the six housing screws and Omnetics connectors were also removed to conserve space. (Note that no electrical tests will be performed in these rabbits). The circuit board was also clipped down to fit into the housing.

Additional changes were made to the design to optimize the ability of the ribbon cables on the microelectrodes to flex with the pulsations of the brain. The lumen area is now filled with artificial cerebral spinal fluid (aCSF), covered by a customized glass plate and sealed off from the external environment with a new biocompatible silicone elastomer. This permits the probes and ribbon cables to flex and bend with the pulsations and micro-movements of the brain, an aspect that the previous design did not take into consideration. The glass plate also allows for observations of the probes, cables, aCSF, and lumen area to be made post-operatively.



1: Received voltage at the input
2: Recovered clock
3: Demodulated data

(a)



1: Outgoing raw data
2: Modulator output
3: Transmitter output
4: Current through the transmitter coil

(b)

Fig. 9: Simulated waveforms for (a) send and (b) receive data paths

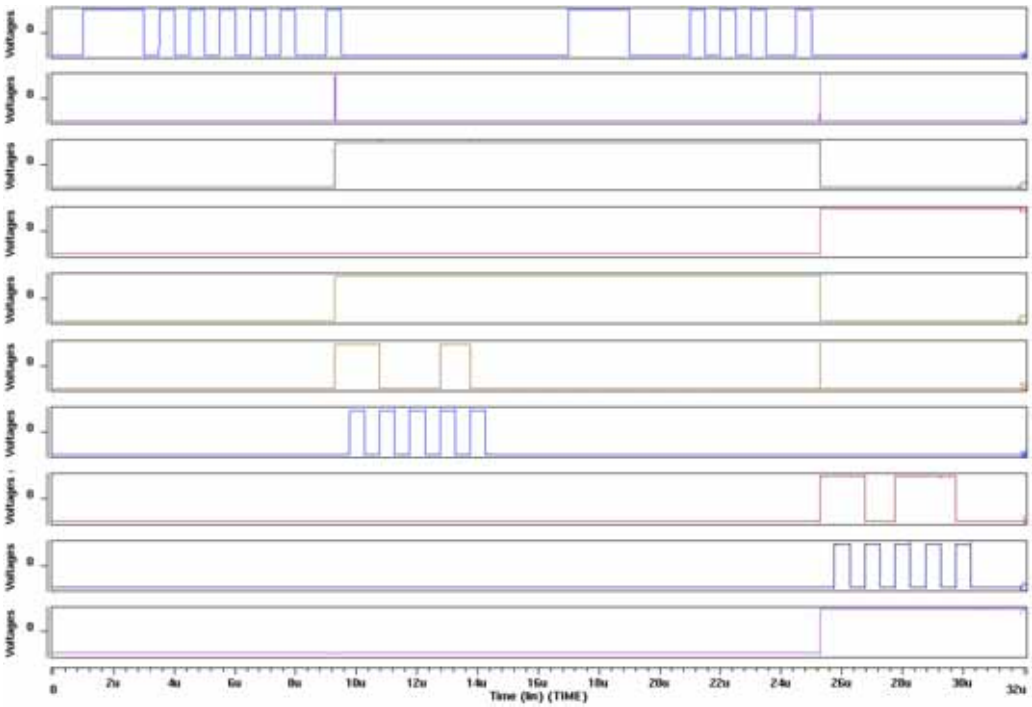


Fig. 10: Simulated operation of the DICL

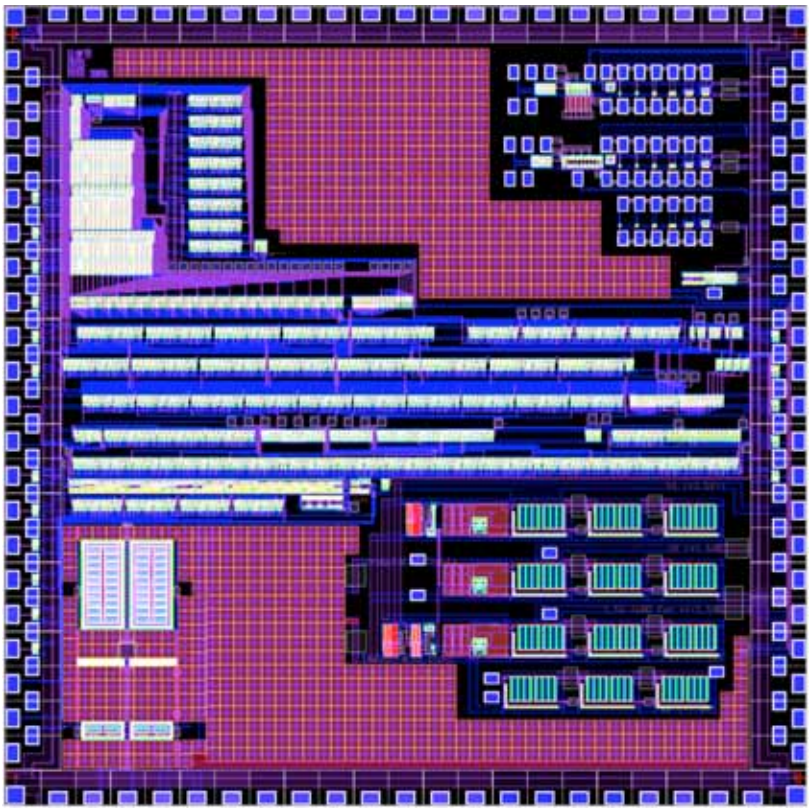


Fig. 11: Layout of the BTT

Finally a biologically inert silicone elastomer port was developed and implemented in the design by filling a shortened corner on the glass plate with NuSil. The shortened corner allowed enough space for two 25- gauge needles to provide access to the lumen to bleed out any remaining air bubbles, fill with additional aCSF, or eventually permit a way to apply drugs directly to the brain.

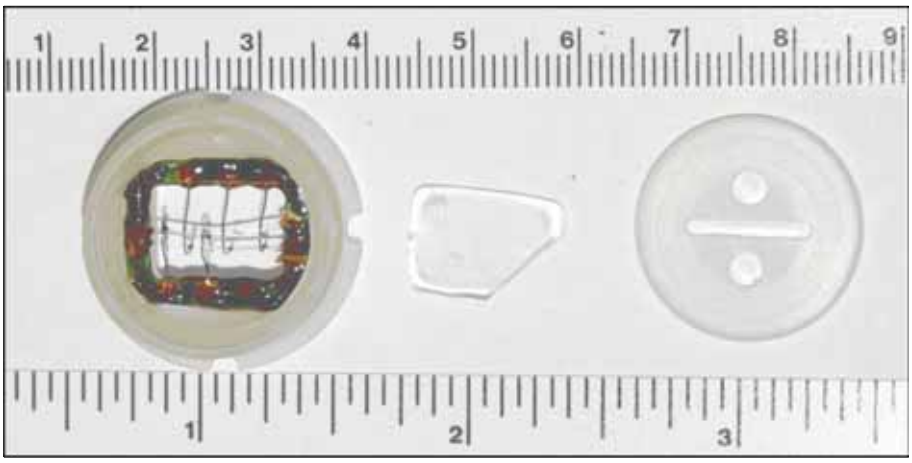


Fig. 12: Current Design (A) MINI 3.1, (B) lumen covering glass slide with shortened corner for fluidic port, and (C) lid of MINI 3.1.

Design Modifications from MINI-2 to MINI-3 (Fig. 12):

- *Scaled down housing diameter:* The diameter of the circular housing wall was reduced from 39.5 mm to 23.5mm to fit on the cranium of the rabbits for *in vivo* testing. This reduction required the circuit board to be cut down in size, removing the six housing screws and the six Omnetics connectors from the design also.
- *Artificial CSF:* The lumen was filled with aCSF, replacing the silicone elastomer and dental acrylic. The aCSF allowed the electrodes to move and flex with the brain, whereas the silicone elastomer and dental acrylic appeared to fix the probes in place.
- *Glass plate lumen cover:* The lumen was covered by a customized glass plate to create a hydrostatic pressure chamber that kept all fluids in the lumen and allowed for visualization into the lumen. One corner of the plate had been removed prior to surgery to allow for the fluid port to be fully functional post-surgery.
- *NuSil Silicone Elastomer:* NuSil silicone elastomer replaced Kwik-Sil silicone elastomer due to its more extensive biocompatibility testing and better mechanical properties.
- *NuSil fluid port*: A NuSil-filled fluid port was implemented into the design so as to allow a way to directly manage the fluid in the lumen whether it is to replace with new aCSF, bleed out new or remaining air bubbles, or even to apply drugs directly to the brain.
- *Lid tool shape and fittings*: An additional pattern was added to the lid of the system to improve the ease of opening and permitted opening with alternative devices (e.g. flathead screwdriver) in case the opening tool was unavailable.

- *Attachment notches*: Durable attachment notches were added on to the bottom of the external housing wall to provide an additional media for the dental acrylic to grip to, preventing the MINI from moving or rotating.

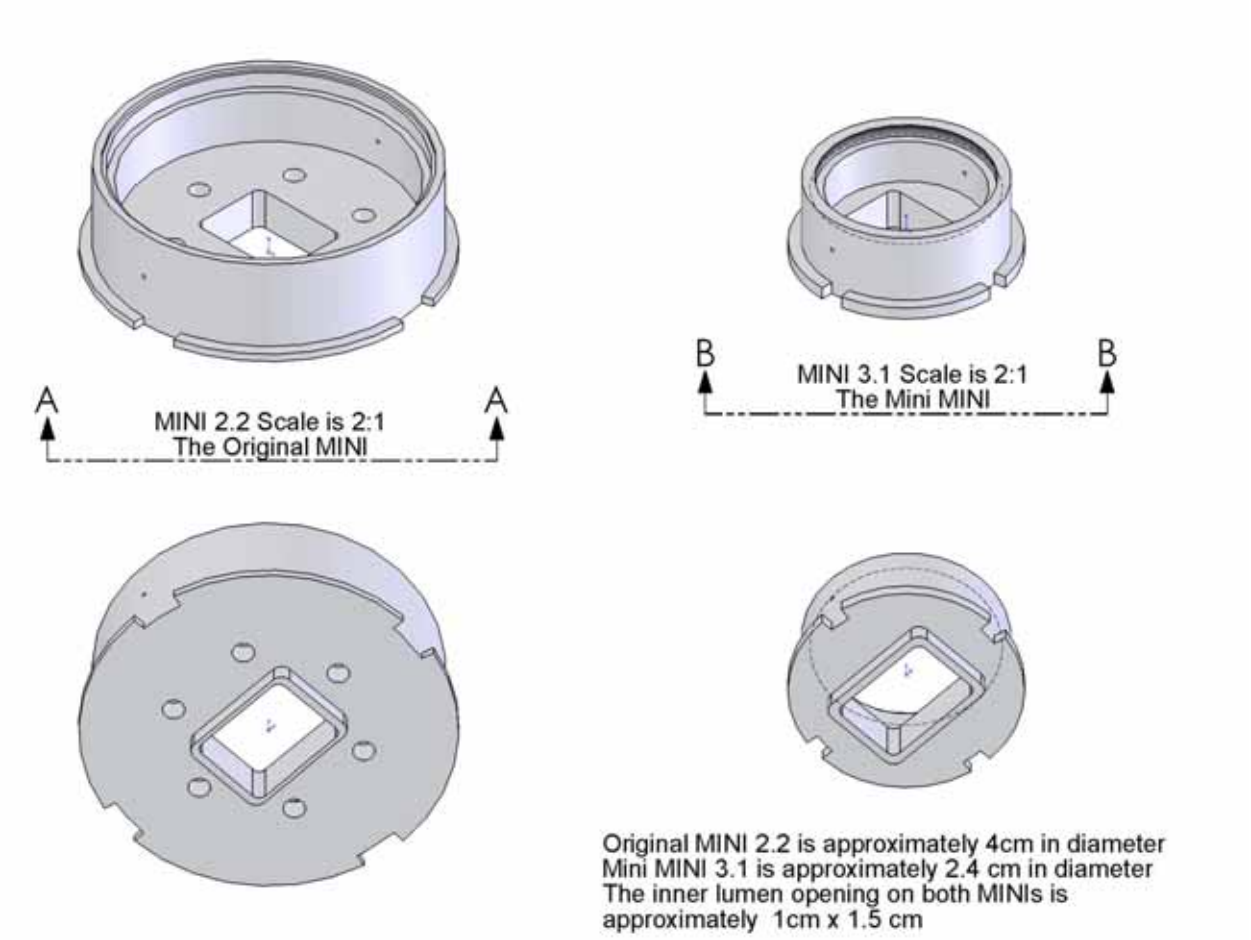


Fig. 13: (A) Original MINI – MINI 2.2 (B) Modified housing design – MINI 3.1

Fluidic Bench Tests:

Bench tests were conducted to test the sealing properties of a silicone elastomer (MED2-4220 - NuSil, Carpinteria, CA) when used to attach the MINI housing to the skull and also the glass cover to the circuit board. Simulated craniotomies were created using acrylic containers, whereby the MINI was "implanted" using the simulated surgical techniques. The glass cover was attached using silicone, with enough space for insertion of two 28-gauge needles (inlet, outlet ports). After letting the silicone cure for approximately 4–6 minutes, the two needles were inserted and fluid was injected until all trapped air was removed. Afterwards, additional fluid was injected to increase the hydraulic pressure, meanwhile the system was visually observed for the presence of leakage. After fluid injection, the needles were removed, and the precise location of needle injection was monitored for fluid leakage.

The simulated system was consistently able to withstand pressures up to 60MPa before any signs of fluid leakage occurred. This level of hydraulic pressure is considerably beyond the level of human intracranial pressures, which is approximately 0.1MPa. Also, the system was able to contain high pressures (50–60MPa) indefinitely upon removal of the needles. These results demonstrated the system would sufficiently seal the intracranial environment from the outside world.

Rabbit Experiments:

Rationale: Rabbit models were chosen to evaluate the biocompatibility and toxicity of materials (silicon, polysulphone, silicone elastomer) and to develop novel surgical techniques for optimal implantation of the MINI. These animal experiments provide a means for rapid turnaround of data to allow for adequate numbers of observations to provide data necessary to make clear interpretation of results.

Surgical Techniques: Probes were implanted into sensory and motor cortices of each animal model. Following the creation of a 9mm x 13mm craniotomy, the dura was resected up to the edge of the bone and aCSF was applied to maintain a well-hydrated environment. A thin layer of silicone was applied to the top surface of the bone around the perimeter of the craniotomy. This was used to create a water-tight seal preventing any post-op fluid leakage. A thin layer was also applied to the bottom side of the MINI immediately prior to final placement on the skull. The MINI was positioned inside the craniotomy. This was done prior to complete polymerization of the silicone. A small amount of dental acrylic was applied between the MINI and nearby bone screws to help stabilize the device. Each 16-channel probe was hand-inserted through the pia using a custom designed insertion tool. Afterwards, a thin layer of silicone was applied on the circuit board around the perimeter of the inner lumen. A custom-made glass cover was positioned over the lumen, and sealed with silicone. One corner of the glass cover was "trimmed" to allow for fluid access to the lumen. This void was filled with silicone. Once the silicone cured, it acted as a membrane allowing fluid access to the lumen. Two 28-gauge needles were subsequently used to penetrate this access port: one for fluid injection, and one for bleeding trapped air. The inner lumen was completely filled with aCSF such that the implanted probes were able to "float" with the brain. A polysulphone screw-in cap was used as an extra measure to protect the inner components of the MINI from normal animal behaviors.

Surgical Implant Results: At the time of this writing, a series of 1-month implant procedures have been completed. The inner lumen was inspected periodically throughout the implant duration and no signs of fluid leakage were present. The chamber remained completely filled with fluid without the presence of air (Fig. 14). Results demonstrated that our techniques provided a sufficient hydrostatic seal. Tests conducted under anesthesia and postmortem revealed that the fluid within the inner lumen could be completely replenished with ease using two needles (inlet/outlet ports), as described in the methods section.

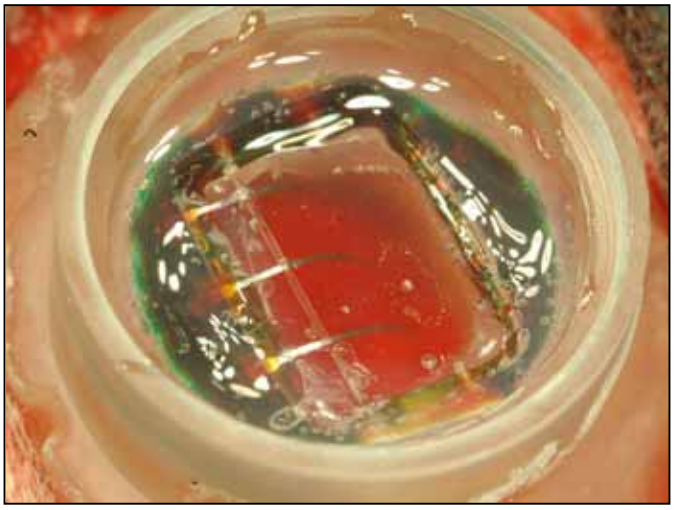


Fig. 14: Scaled down version of MINI implanted in rabbit motor cortex.

The probes and cables were visually inspected throughout the implant duration for breakage and/or withdrawal out of the cortex. Without mechanical support of the cables, as was done in previous experiments using Gelfoam, ALGEL, or Kwik-Sil, we were uncertain whether the silicon would remain intact over long-periods. In all cases, each cable remained unbroken through the implant duration. We were also concerned that pulsations of the brain might gradually push the probes out of the tissue. It appeared that once the chamber was filled with fluid and a hydrostatic equilibrium was created, the brain pulsations diminished and were no longer a factor.

Another potential attribute of this design is the ability to visualize the surface of the brain over extended periods. As seen in Fig. 14, the fluid in the chamber mixed with blood making the surface of the brain no longer visible. To avoid this problem, we are taking extra precautions to minimize any bleeding and also removing any blood in the nearby region. In cases where extensive mixing of blood and aCSF occurred, the red blood cells seem to gradually settle to the surface of the brain. This results in a more translucent fluid, however still tinted red. If this region can be managed properly, there is a large potential for this approach to be used for other types of applications, in addition to electrophysiological studies.

Next Iteration:

We have plans to perform a replacement procedure on the second implant near the end of April. This will consist of replacing the PCB and the implanted probes. We also have plans to perform a third surgical implant in a monkey in May. In this design, the six 18-pin Omnetics plastic connectors (susceptible to breakage) will be replaced with two robust high-density 51-pin Omnetics metal-encased connectors. This connector is more

mechanically sound and will only require the experimenter to make two connections, rather than six connectors as in the previous versions.

The external housing will also be altered to accommodate for the change in connector design by taking on a more rectangular shape. A variety of different types of lids and closing methods are and will be investigated, tested *in vitro*, and optimized for our needs. The next generation will be fabricated in commercially pure titanium, ideal for stimulating bone regrowth around the MINI.

Rabbit testing will continue, with a focus on the surgical techniques used to adhere the MINI to the cranium, inserting the probes, minimizing the effects of the destructive nature of dural regrowth, and the use of alternative antibiotics and anti-inflammatory drugs pre- and post-operatively to improve the tissue response around the probes.

Concerns

During the past quarter of this contract, we have generally followed the plan outlined in the original proposal and have met most of the milestones described there. We have made good progress in the probe area, designing and fabricating a new set of passive structures for monkey motor cortex, and designing a non-multiplexed version of our 64-site active structure. We have completed test versions of our spike detector chip and our bidirectional wireless probe interface and will iterate these into implantable devices during the summer. Design of the microsystem implant assembly continues to be a challenge, and we are working in rabbits to perfect the assembly and associated surgical techniques before returning to monkey implants next month. The development pace is fast, but we are on-track for chronic monkey implants of the complete system before the end of the year.

Conclusions

During the past quarter, we have designed and fabricated new 16-site multi-shank passive probes that are optimized for use in monkey motor cortex. Additional passive probes for use in studies of chronic tissue reaction have also been realized. Our 64-site active probe has been redesigned for non-multiplexed operation and the amplifiers have been optimized for improved dynamic range. They still offer an overall gain of 1000 and bandwidth from an adjustable lower cutoff (1-100Hz) to 10kHz and allow site testing on demand.

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